Paul Krogstad, MD: UCLA IRB #01-11-064
" HIV Replication and Thymopoiesis in Adolescents with HIV"

UCLA response to questions from Robert Nelson, MD:

1. The IRB minutes and administrative letter requesting a 407 panel review are insufficient to determine the reasons that the IRB was unable to approve the research under categories 404-406. The letter suggests that the absence of a condition for the HIV-negative adolescents was the reason for not approving the sub-study under 406. However, the substudy was not given limited approval for enrolling the adolescent HIV-positive subjects.

A: The investigator withdrew consideration of the substudy with minors pending review by the DHHS Secretary's Panel as the scientific design required a matched comparison control group.[1] ***The proposed research procedures were seen as a minor increase over minimal risk for all subjects. The study was subsequently IRB approved restricted to adult subjects.***

2. From the inclusion of control subjects in the main study, it would appear that the IRB considered the chest CT scan to be minimal risk. However, there is no analysis of the risks of the CT scan, other than the comment in the consent form that the radiation exposure is equal to about 16 months of background radiation. This would suggest that the chest CT scan has an exposure of about 400 mrem. However, there is no documentation or letter from the radiation committee confirming this determination.

A: Medical Radiation Safety Committee (MRSC) approval was obtained 7/23/02: see 2/27/03 revised IRB approval notice included in 7/22/02 letter to Dr. Carome. The MRSC approval letter is available for your review.

3. The documentation also fails to indicate whether the 24 hour IV infusion was considered a "minor increase over minimal risk", although this can be inferred.

A: The procedures, in their entirety, for the control subjects as well as the HIV+ subjects were considered more than a minor increase over minimal risk. Please see further explanation below in response to #5.

4. The administrative letter also refers to "radioactive materials." However, the deuterium is a stable isotope and thus is not radioactive.

A: Agreed.

5. We should have clarification of the exact risk determinations for the separate interventions and procedures contained in the research,

[1] See February 21, 2002 and May 13, 2002 correspondence from P. Krogstad to R. Figlin included in July 22, 2002 packet to Dr. Carome.

a. specifically the chest CT scan,

b. 24 hour IV infusion,

c. the dextrose concentration (which is not specified) and the deuterium-containing water.

A: It may be we do not understand the question or the purpose of the question. It is our understanding that the IRB is required to make a risk determination based on all of the proposed procedures in the project. In this research, the Board assessed the risk to all subjects, but paid particular attention to the control subjects, who by definition, have no condition under study, and are therefore, restricted in their participation in more than minimal risk research by the Federal regulations.

45 CFR 46.406 requires that the research be "likely to yield generalizable knowledge about the subject's disorder or condition." ***Additionally, the regulation requires*** "the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition…."[2]

As noted above, the control subjects do not have "a disorder or condition" ***and the proposed research interventions present experiences that are more than minimal risk, that is, the research includes procedures that are not "***ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests."[3] ***We recognize the importance of addressing the*** "more than a minor increase over minimal risk" ***requirement in 46.406 for all minor subjects in the proposed research. Unfortunately, neither the regulations or the OHRP guidelines provide assistance in determining the nature of or describing a*** "minor increase over minimal risk."

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[2] §46.406 Research involving greater than minimal risk and **no prospect of direct benefit to individual subjects, but likely to yield generalizable knowledge about the subject's disorder or condition**. DHHS will conduct or fund research in which the IRB finds that more than minimal risk to children is presented by an intervention or procedure that does not hold out the prospect of direct benefit for the individual subject, or by a monitoring procedure **which is not likely to contribute to the well-being of the subject**, only if the IRB finds that:

(a) the risk represents a minor increase over minimal risk;

(b) **the intervention or procedure presents experiences to subjects that are reasonably commensurate with those inherent in their actual or expected medical, dental, psychological, social, or educational situations;**

(c) **the intervention or procedure is likely to yield generalizable knowledge about the subjects' disorder or condition which is of vital importance for the understanding or amelioration of the subjects' disorder or condition**…."

[3] 45 CFR 46.102(i) Minimal Risk: the probability and magnitude of harm or discomfort anticipated in the research are not greater in and of themselves than those ordinarily encountered in daily life or during the performance of routine physical or psychological examinations or tests.

Though it may be possible to make a risk determination for each procedure, such determinations for individual procedures seem of little help in determining an overall risk assessment for the subjects or the subject population. For example, a clinical trial may include procedures such as a providing an experimental drug and a small blood draw. Though the small blood draw may be considered minimal risk, such a determination is of little importance in determining whether the drug administration is more than minimal risk. 45 CFR 46 at least implies if not compels the IRB to make a risk determination regarding the collective nature of the research procedures and not necessarily parse out assessments of individual procedures.

For example, the regulations do not indicate a "procedure by procedure" risk assessment as necessary to making a risk assessment regarding the proposed research:

§46.403 **IRB duties.**

"In addition to other responsibilities assigned to IRBs under this part, each IRB shall review research covered by this subpart and approve only ***research*** which satisfies the conditions of all applicable sections of this subpart" [emphasis added].

45 CFR 46.111(a)

(1) Risks to subjects are minimized: (i) by using procedures which are consistent with sound research design and which do not unnecessarily expose subjects to risk, and (ii) whenever appropriate, by using procedures already being performed on the subjects for diagnostic or treatment purposes.

(2) Risks to subjects are reasonable in relation to anticipated benefits, if any, to subjects, and the importance of the knowledge that may reasonably be expected to result. In evaluating risks and benefits, ***the IRB should consider only those risks and benefits that may result from the research*** (as distinguished from risks and benefits of therapies subjects would receive even if not participating in the research). The IRB should not consider possible long-range effects of applying knowledge gained in the research (for example, the possible effects of the research on public policy) as among those research risks that fall within the purview of its responsibility [emphasis added].